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16. ABSTRACT

The present chapter covers the individual and combined neurobehavioral effects of four of the major products of combustion. They are carbon monoxide, hydrogen cyanide, carbon dioxide and hypoxic hypoxia. The effects of each were reviewed separately and then the literature of the effects of combined exposures were covered. The latter is a relatively sparse literature. The empirical and physiological information available was encoded as a series of dose-effects and pharmacokinetic equations. Assuming additive effects, a mathematical model was proposed for the combined exposure. Several pharmacokinetic intera ctions make the received dose of the combined pollutants non additive, however, and thus introduce nonadditivity into the combined model. The model was useful in pointing out the kind of information still needed to make predictions. The model thus serves a mainly hueristic purpose.

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EFFECTS OF ATMOSPHERIC MIX AND TOXIC FUMES ON MILITARY PERFORMANCE[1]

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TABLE OF CONTENTS

	PAGE
INTRODUCTION	1
THE CONTAMINANTS IN QUESTION	5
EFFECTS OF INDIVIDUAL CONTAMINANTS	6
CARBON MONOXIDE (CO)	6
Pharmacokinetics	6
Mechanism of Action	9
CNS and Behavioral Effects	10
Brief Review of Literature	10
Synthesis and Hypotheses	12
HYDROGEN CYANIDE (HCN)	16
Pharmacokinetics	16
Mechanism of Action	19
CNS and Behavioral Effects	20
Lethality	20
Non Lethal Effects	21
Electrophysiology	23
CARBON DIOXIDE	23
Brain Effects	24
Cerebral blood Flow and Metabolic Rate	24
Electrophysiology	25
Effects on Respiration	26
Task Performance	27
HYPOXIC HYPOXIA	28
Mechanism of Action	29
Behavioral Effects	30
Sensory	30
Vigilance	31
Psychomotor	32
Cognitive and Reaction Time	32
Summary	32
REVIEW OF EFFECTS OF COMBINATIONS OF INHALED SUBSTANCES	33
CARBON DIOXIDE AND HYPOXIC HYPOXIA	33
CARBON MONOXIDE AND HYDROGEN CYANIDE	34
CARBON MONOXIDE AND HYPOXIC HYPOXIA	35
A PREDICTION MODEL FOR COMBINATIONS OF THE TOXIC GASSES	36
GENERAL CONSIDERATIONS	37
Forms for Individual Toxicants	37
Minute Ventilation Effects	40
EFFECTS OF COMBINATIONS OF SUBSTANCES	41
Additivity and Synergism	41
Combined Exposure Model	42
DISCUSSION AND CONCLUSIONS	43
SUMMARY POINTS	43
EXPOSURE SAFETY GUIDELINES	46
Single Substance Exposure	46
Multiple Substance Exposure	47

EFFECTS OF ATMOSPHERIC MIX AND TOXIC FUMES ON MILITARY PERFORMANCE

Vernon A. Benignus

INTRODUCTION

Both training and combat scenarios in military settings, frequently expose military crewmen to mixtures of fumes, many of them potentially toxic. One of the most common mixtures is that of combustion products. Products of combustion originate from diverse sources such as burning of projectile propellants, exploding munitions, fires burning in the environment, vehicle exhausts, etc. The concentration and composition of such toxic gasses vary widely depending upon such factors as the material being burned, the amount of oxygen available to the combustion, the adequacy and operation of ventilation systems, etc.

In addition to the concern for the short and long term general health of military personnel, there is legitimate concern for the effects of such exposures upon performance of tasks. If exposure to the toxicants affect the central nervous system (CNS), even temporarily, there could be widespread effects other than on the general health and well-being of the exposed person. If the exposed person's task performance is impaired, errors or delays on his part could reduce the effectiveness of crew performance and affect the survival of the person and those who are dependent on him. Large and obvious impairments are clearly of concern, but even small decrements are of potential interest in performance of critical or marginal tasks. The effects of

mixtures of toxic gasses are of interest in a wide variety of settings both in and outside the military.

Most of what is known about the effects of toxic gasses on performance is the result of laboratory experimentation. It is not always logically easy to relate such laboratory results to performance of non-laboratory, e.g. military tasks. The easiest way to extrapolate to non-laboratory situations, e.g. military performance, is to appeal to the presumed factor structure of the task in the field. Military tasks are presumed to require basic behavioral and sensory abilities such as reaction time, accuracy and stability of movement, alertness, sensory sensitivity and perceptual accuracy. Some tasks involve more of certain abilities than of others. Thus if a substance has been shown to impair e.g. visual sensitivity, then performance of field tasks requiring such sensitivity would be expected to be impaired. The extent of the impairment is not readily estimated, however. The problems with quantitative extrapolation from laboratory to field performance have been discussed by Chapanis (1967). In any practical situation, decisions must often be made by the judgment of persons most intimately familiar with the particular applied task as well as the results of laboratory work.

Writing of the effects of mixtures of toxic fumes on performance is a speculative task. The effects of some individual gasses on performance are understood in a limited empirical sense. There is also sufficient theory to guide conjecture about the effects of some of the substances in combination. But, there are few data regarding effects of multiple, simultaneous exposures.

What data exist on the effects of simultaneous, multiple substance exposure are frequently on the topic of incapacitation or lethality. While these data are valuable in themselves, they are difficult to generalize to lower levels of exposure. This is because levels of exposure near the incapacitation point frequently have begun to affect multiple body functions, not the first ones to be affected by lower-level exposure. At the higher levels of exposure, then, the body functions affected first, by low-level exposure, may already be asymptotically affected so that interactions between substances may no longer matter or may matter much less. Similarly, body functions less sensitive to disruption may then give a quite different picture of disruption, leading to confusion rather than accurate extrapolation. Thus, the data about the effects of multiple gas exposure on lethality and incapacitation will be used in a very circumspect manner in the present review.

The procedure in this chapter will be to (a) review data regarding the effects of individual substances or conditions (b) review data from experiments in which combined exposures were used (c) summarize the current knowledge in a mathematically expressed model and (d) give some guidance to personnel responsible for safety and performance in the presence of such exposures. The latter guidance is expressed in terms of factors of task performance, not actual military tasks. The user of the data can best make judgments regarding the applicability of the factors to the many military tasks to which the data might apply.

A mathematical model was constructed to predict the central nervous system (CNS) and/or behavioral effects of each substance by itself. The model-building strategy was to (a) express the behavioral effects as a function of body burden (blood levels), (b) incorporate a sub-model for prediction of body burden in terms of exposure levels and/or physiological variables as predictors and (c) combine the effects of the individual substances into a single model. The model building process was a sometimes empirical, sometimes theoretical process. Where theory was available, it was used. If theory was not extant, empirical curves were used. The model is considered as a provisional mathematical encoding of present knowledge with a considerable amount of extrapolation and conjecture to fill in gaps.

What results from the above is a skeleton without flesh. The proposed model yields no specific predictions. Instead it shows form and relationships. The model is intended to be heuristic in the broadest sense; to suggest what kinds of data are needed and where they are to be fitted so that specific predictions may be made. By use of straw-man coefficients, the model can be used in simulation experiments to predict shapes of dose-effects curves. When the specific data become available, the model may be used to estimate safe levels of gas exposure combinations for specific tasks, to generate predictions of numbers of effects of a particular magnitude, etc.

The predictive model was stimulated by the work of a broad community of scientists who have published their work elsewhere. The intent of the models of this chapter was to bring the labor of others together with additions and modifications. More

importantly, the chapter will be used to evaluate and delimit the scope of the predictions.

THE CONTAMINANTS IN QUESTION

Attention will only be given to a subset of the products of combustion. Examples of the kinds of combustion to be considered are the gasses produced by burning projectile propellants, *e.g.* breech gasses of weapons, and the products of fires. Of course, there are endless differences in the details of the composition of the gasses in question, depending on such factors as the composition of the burning material, the rate of burning and the available oxygen (O_2), to mention but a few. Sufficient similarity exists, however, to make general coverage of combustion products a possible topic. A few substances are found in considerable quantity in most mixes of toxic combustion products.

Emission gasses from the M16 rifle, an XM2 Infantry Fighting Vehicle, an M198 howitzer and the MLRS (Multiple Launch Rocket System have been analyzed in detail (Snelson *et al.*, 1983; Ase, *et al.*, 1985). The products of fires have also been extensively characterized (Levin *et al.*, 1987; Purser, 1986) under a wide variety of conditions. Gasses known to have effects on the CNS and/or on performance and which appear in most of the mixes are carbon monoxide (CO), carbon dioxide (CO_2), sometimes hydrogen cyanide (HCN) and a host of chemicals of which little is known other than that they are sensory irritants. examples of irritants are aldehydes, hydrochloric acid, phosgene and ammonia to name but a few. Another condition frequently found in atmospheres

contaminated with fire products is a reduced level of oxygen (O_2).

For the purpose of simplification of the problem, the contaminants to be considered are restricted to those listed in Table 1 along with a brief statement of the supposed mechanism by which they produce their behavioral or CNS effects. Most of the entries in Table 1 are self-explanatory. The last category is a catch-all to classify diverse substances by one common attribute, sensory irritability. While there may be other effects of these substances than irritability, such effects are probably small compared to the effects listed in Table 1, especially at comparatively low concentrations. To avoid complexity, the effects of irritants will not be extensively discussed in this chapter.

Things are not as simple as made to appear in Table 1. A number of the substances are suspected of having other mechanisms of action in addition to those listed. Also, small effects are ignored in the table for simplicity. Such simplifications will also be carried into the model. In each case in the subsequent discussion where simplifying assumptions are made, the assumptions will be stated explicitly.

Insert Table 1 about here

EFFECTS OF INDIVIDUAL CONTAMINANTS

CARBON MONOXIDE (CO)

Pharmacokinetics.

CO is a clear, colorless, odorless gas which is the product of incomplete combustion. It enters the body by inhalation and is diffused across the alveolar membranes with about the same ease as is O_2. The coefficient of diffusion is a function of active alveolar area and perfusion by pulmonary vasculature. Upon crossing the alveolar membrane, CO is dissolved into the blood and quickly becomes bound to hemoglobin to form carboxyhemoglobin (COHb). Thus CO competes with O_2 which would normally form oxyhemoglobin (O_2Hb). While CO and O_2 bind hemoglobin almost equivocally, CO is bound about 245 times more firmly than is O_2 (Sendroy et al., 1929; Joels and Pugh 1958; Rodkey et al., 1969; Longo, 1970; Roughton, 1970, Joumard et al.; 1981). Thus COHb can accumulate and block the formation of O_2Hb.

The formation of COHb has been described by a differential equation model based on first principles (Coburn, Forster and Kane, 1965). A complete discussion of the model is not needed here because it is well described elsewhere. The so-called Coburn-Forster-Kane equation (CFKE), not given here, gives a COHb prediction of the form;

$$\frac{d(COHb)}{dt} = f(\text{ppm CO}, \dot{V}_A, \text{other physiological variables}) \quad [1]$$

in which;

$\frac{d(COHb)}{dt}$ = the rate of COHb formation over time (t)

ppm CO = the concentration of CO in inspired air in ppm

$\dot{V}_A$ = alveolar ventilation rate

other physiological variables are beyond the scope of this chapter.

The variable in the CFKE which merits additional discussion in the present context is $\dot{V}_A$, alveolar ventilation rate. $\dot{V}_A$ is a measure of the air exchange in the functional alveoli which is determined by pulmonary ventilation, among other variables. Thus, any variable which will increase pulmonary ventilation, e.g. physical exercise, heat, arousal, etc., will increase COHb formation rate via increased $\dot{V}_A$.

Figure 1 is a graph of COHb formation in humans as a function of time for a fixed CO exposure level (100 ppm) and for two levels of $\dot{V}_A$. The data for Figure 1 were generated by a CFKE computer program. COHb continues to increase over a long period of time as an exponential function. The effect of increased $\dot{V}_A$ is to increase formation rate, not asymptotic level.

Insert Figure 1 about here

A method of estimating $\dot{V}_A$ in a particular military situation has been developed by Steinberg and Nielsen (1977). The procedure involves categorization of amount of work being performed by the subject while exposed to CO. Knowledge of workload allows estimation of ranges of $\dot{V}_A$ for healthy young males. Workload can, in turn, be estimated from the military task that a crewman is performing. The method is fully specified in the U.S. Department of Defense, Human Engineering Standard (MIL-STD 1472) and U.S. DOD MIL Handbook 759.

The CFKE model for COHb formation has been tested by Peterson and Stewart, 1970; Stewart et al., 1973; Peterson and

Stewart, 1975; Joumard et al., 1981. The predictions appear to be good in most cases. In many tests, the researchers found it necessary or convenient to use mean values for the majority of the physiological coefficients rather than measuring them on individual subjects. It is not clear whether observed prediction errors were due to an inappropriate model (the CFKE) or whether physiological variables differed from those assumed. For the present purposes, the CFKE appears to be the best and most accurate method available for prediction of COHb. A modified version of the CFKE permits easier mathematical manipulation of the expression (Muller and Barton, 1987).

Mechanism of Action.

Under certain conditions it is widely held that the effects of CO exposure are due to the hypoxic effect produced by the reduction of hemoglobin available to carry O_2 (Coburn, 1979), referred to as the CO hypoxia hypothesis. The effects under this hypothesis should be directly related to COHb.

CO dissolved in blood (not yet bound to hemoglobin) is toxic to certain cytochrome activity (Piantadosi et al., 1987). In most exposures, little dissolved CO would be delivered to tissue by the blood since COHb is so rapidly formed. If, however, high levels of CO exposures were encountered, it is possible that not all COHb would be taken up by hemoglobin binding and thus some dissolved CO may remain in the blood for a short time (Rumen and Chance, 1970). It is not clear what amount of dissolved CO would remain under what circumstances and for how long. Nor is it known how much CO would have to appear and for how long to produce cytotoxic effects. It should be kept in mind, that the

CO hypoxia hypothesis may not be an exhaustive statement of the mechanism of effects for CO exposure.

CNS and Behavioral Effects.

Brief Review Of Literature. The literature on the effects of elevated COHb on humans is in considerable disarray. This literature has been critically reviewed by Laties and Merrigan (1979) and Benignus et al. (1983). Many of the studies conducted with human subjects were performed at only single, low levels of COHb (below 10%). Studies that reported effects of COHb elevation were not usually confirmable by others. A vigilance study reported by Horvath et al. (1971) demonstrated decrements at COHb levels of 6.6%. However, two attempts to replicate the study, did not obtain significant decrements (Christensen et al., 1977; Winneke, 1974). Another type of vigilance task was affected by exposure to 50 ppm CO for 80 minutes (Fodor and Winneke, 1972). Winneke (1974) used the same task and failed to find significant effects at 50 or 100 ppm for the same exposure time. Exceptions to the above series of nonconfirmations are the two studies of compensatory tracking reported by Putz et al. (1976, 1979). Tracking performance was decremented by a significant but small amount by elevation of COHb to 5%. Benignus et al. (1987) replicated the study and obtained similar results at 8% COHb. A number of single-COHB-level studies were reported in which no effects of COHb occurred. These were reviewed in Benignus et al. (1983).

Dose effects studies of COHb and various neurobehavioral variables with human subjects provide no more stable data base

than the single-level studies (Benignus and Muller, 1988b). Visual dark adaptation was reported to be impaired in a dose-related manner at COHb levels ranging from 4.5 - 19.7% (McFarland et al., 1944; Halperin et al., 1959; McFarland, 1970). The above reports apparently all involved the same experiment, using four highly trained subjects. Other experiments, in some cases much more detailed, failed to find any dark-adaptation effects (Abramson and Heyman, 1944; Hudnell et al., 1988). Beard and Grandstaff (1970) and Seppanen et al. (1977) reported dose-related critical flicker fusion effects at COHb levels up to 7.5 and 12.4% respectively. Others, however found no effects with COHb levels as high as 26% in some cases (Fodor and Winneke, 1972; Guest et al., 1970; Lilianthal and Fugit, 1946; O'Donnel et al., 1971, Ramsey, 1973; Vollmer et al., 1946; Von Post-Lingen, 1964).

Beard and Wertheim (1967) reported dose related decrements in time discrimination beginning at estimated COHb levels of 2.5% and ranging up to 12.5%. Attempts at confirmation consistently failed (O'Donnel et al., 1971; Stewart, 1975; Stewart et al., 1975; Mikulka et al., 1970; Otto et al., 1979). Signal detection, reported to be affected in a dose-related manner (Groll-Knapp et al., 1972) was not affected in similar studies (Groll-Knapp et al., 1978; Haider et al., 1976). Benignus and Muller (1988a) reported that compensatory tracking was decremented in a dose related fashion by COHb levels ranging up to 17%. Only slight effects and a shallow-sloped function were found. There has been no attempt at replication.

The lack of agreement among human studies of COHb effects is perhaps attributable to a number of factors. Poor experimental designs and anticonservative statistical tests were common. Many studies were not conducted in a double blind manner. It is probable that levels of COHb as low as 5%, and perhaps lower, produce small and variable neurobehavioral effects, but large numbers of subjects in carefully designed and executed experiments would be required to demonstrate such effects.

Persons who habitually smoke tobacco have chronically elevated levels of COHb. It is possible that their already elevated COHb level leaves them at greater risk to further elevation. It is also possible that they have adapted to COHb effects by any of a number of bodily compensatory mechanisms. Furthermore, the effects of smoking are not simply to elevate COHb. Other psychoactive substances are involved. The issue combined effects of smoking and toxic fume exposure are far too complicated and unknown to include in the present chapter. The reader should, however, be aware that a potentially serious complication could occur for smokers in the presence of toxic gas exposure.

Synthesis and Hypotheses. Benignus and Muller (1988a,b) recently reviewed and synthesized the literature on dose-effects relationships of COHb vs. several neurobehavioral variables. Their conclusions and arguments are briefly recapitulated here. Meta analyses were performed on the literature concerning dose-effects functions in laboratory animals engaged in bar press and cage shuttling tasks and humans engaged in compensatory tracking.

The human plot of error scores has a similar appearance to the lower-level part of the function demonstrated in laboratory animals. The dose-effects function in man was hypothesized to have the same general shape as that in laboratory animals. There are, however, no data on the COHb levels required to reach or exceed the area of the hypothetical portion of the function in man where large decrements occur. Figure 2 is a plot of dose-effects functions for COHb and inter-response times in laboratory animals, along with a plot of the dose-response function fitted to human compensatory tracking data. The curves are nonlinear positively accelerated functions. The curve for man is extrapolated beyond 20% to illustrate the best available prediction.

Insert Figure 2 about here.

The shape of the dose-effects function can be hypothetically explained as the result of a compensatory mechanism. As COHb is formed, a proportional CNS vasodilation occurs (Paulson et al., 1973; Doblar et al., 1977; Traystman, 1978; Jones and Traystman, 1984). Such vasodilation has the effect of supplying more blood, and hence increasing the O_2 supply to the CNS. Thus, while the O_2 carrying capacity of the blood has been reduced by the formation of COHb, the O_2 supply tends to be maintained by increased flow. The latter acts to offset the CNS effects of COHb and appears to prevent the reduction in O_2 consumption in the CNS (Jones and Traystman, 1984) even for very high COHb levels.

The compensatory mechanism of CNS vasodilation could account for part of the shape of the dose-effects function. Below a critical level of COHb, the compensatory mechanism regulates CNS O_2 supply, thus minimizing neurobehavioral effects. As a hypothetical critical level of COHb is approached, the mechanism possibly begins to approach its limit of compensation. As that COHb level is approached, O_2 supply begins to drop and behavioral effects occur.

The data do not support the simple form of the above explanation, however. Cerebral blood flow continues to increase until COHb values as high as 75%, but cerebral O_2 consumption begins to drop somewhere between 30 and 50% in dogs (Traystman, 1978). Hence, some other effect of COHb must account for the onset of behavioral impairments and reduction in O_2 consumption. Account must be taken of the fact that the presence of COHb shifts the oxyhemoglobin dissociation curve to the left thus making O_2 delivery to tissue more difficult (Roughton 1964). It has also been shown that compensatory vasodilation is not uniform in all parts of the CNS and thus some areas might become hypoxic even though whole-brain O_2 consumption is not affected (Koehler et al.). Finally, it is possible that CO dissolved in blood is sufficiently histotoxic to interfere with tissue respiration, thus preventing utilization of delivered O_2 (Piantadosi, 1987).

It is important to recognize the limitations of the state of knowledge in the area of neurobehavioral effects of COHb. The entire shape of the dose-effects function in humans over a wide range of COHb values has not been demonstrated. The entire data

base is derived from laboratory animal experiments except for the part of the function below ca. 17% COHb. Even the lower portion of the curve is known only from highly limited work in man and is subject to legitimate dispute.

The majority of knowledge about compensatory CNS vasodilation originated from work with laboratory animals. The response has not been observed only rarely in man. If the CNS vasodilation is to be used to account for the hypothetical shape of the dose-effects function, it remains to be demonstrated that the response occurs in proportion to the COHb formation in man and it must also be shown that a limit is reached in the compensatory ability to supply available O_2 at the same time as the postulated increased slope of the behavioral function occurs.

In laboratory animals, it is not known how long CNS vasodilation will persist in the face of constant elevation of COHb. It is possible that the response is phasic, and will diminish in effectiveness over time. It is unknown whether the response is impaired by other pharmacological agents or pollutants. The phenomenon must be studied in man as well as in laboratory animals.

Small effects which seem to be the rule in healthy, young persons below at least 17% COHb, do not imply that the effects are of no importance. In performance of tasks which are highly demanding or which can only be performed with marginal success, such small decrements may become important. Thus, while the person may be unimpaired for purposes of most tasks, performance may fail in critical tasks due to a barely raised decrement in ability. If, in fact, the small impairments due to COHb are

verified, it may be necessary to consider the nature of the task in order to decide on critical values of COHb.

No data are available in the literature concerning the possibility of subject-related differences in sensitivity to the effects of elevated COHb. It is not illogical that substantial differences between individuals might exist because such differences have been demonstrated with respect to other pollutants. If individual differences play an important role in the effects of COHb elevation, for safety the exposure danger might have to be evaluated for the most sensitive subjects.

HYDROGEN CYANIDE (HCN)

Pharmacokinetics

The chemical and physical properties of HCN are given in detail by the U.S. Environmental Protection Agency (1988). One of the many synonyms for HCN is hydrocyanic acid, usually applied to the liquid phase. The boiling point of HCN is 25.7°C so that it is in the gas phase for many human exposures of interest. In either phase the substance is colorless. Although there are many environmental sources, HCN is formed as a byproduct of combustion of natural and synthetic nitrogen-containing polymers, *e.g.* wool, silk, nylon, polyurethane, melamine resins, polyacrylonitrile, etc. (Summer and Haponik, 1981). Small amounts of HCN are present in cigarette smoke, automobile exhaust from malfunctioning catalytic converters and the petrochemical industry (Way, 1984).

The olfactory threshold of HCN is *ca.* 5 ppm in air for most persons, although a small number of people are insensitive to its

odor even at lethal concentrations (Sax, 1984; Jenks, 1979). Tobacco smokers may be more sensitive than normal to the odor (Fieser and Fieser, 1967). The odor is similar to that of bitter almonds.

HCN is most readily absorbed via inhalation, but also through the skin (Towill et al., 1978). Following absorption, HCN is rapidly distributed throughout the body via the blood stream. The cyanide ion is responsible for the physiological action of HCN so that the various soluble inorganic cyanide salts share the toxicity of HCN. Once in the blood stream, cyanide (CN) is (in small measure) excreted by the lungs unchanged. The major detoxification route is via conversion to thiocyanate in the presence of sulfur donors. The latter is mediated by the enzyme, rhodanese. Thiocyanate is eliminated via the urine (U.S. Environmental Protection Agency, 1988).

No physiologically-based quantitative models of HCN uptake and elimination, similar to the CFKE for CO, were found in the literature. An empirical equation based on pulmonary parameters was, however, devised for the purpose of predicting lethality of inhaled HCN from the lethality of injected cyanide (Moore and Gates, 1946; Bright and Marrs, 1984) . The model can be used to predict blood levels of CN based on exposure to HCN.

The equation which Moore and Gates devised for prediction of 50% lethal dose (LD_{50}) due to inhalation from the value of the LD_{50} due to injection is

$$VaC - DT = K \qquad [2]$$

in which;

V = the volume of inhaled air (l/kg)

a = empirical proportion of inhaled gas absorbed

C = concentration of HCN in inhaled air (mg/l)

D = empirical rate of detoxification (mg/kg/min)

T = duration of exposure (min)

k = LD_{50} due to injected cyanide (mg/kg).

The value of the term, a, has been estimated as 0.7 and the value of D as 0.017 mg/kg/min (Moore and Gates, 1946, Bright and Marrs, 1984).

Since K is a blood cyanide (BCN) level, the equation can be used to estimate BCN for any given level of HCN in air. For convenience, the inhaled air volume is better expressed in terms of minute ventilation ($\dot{V}_E$) per kg so that

$$V = \frac{\dot{V}_E}{W} T$$

in which W is the subject's weight in kg. Equation [2] may then be rearranged and the above substituted for V as follows;

$$(BCN) = a \frac{\dot{V}_E}{W} TC - DT$$

in which (BCN) = blood cyanide level (mg/kg). Now factoring;

$$(BCN) = T \left\{a \frac{\dot{V}_E}{W} C - D\right\}. \qquad [3]$$

The term BCN in equation [3] is an asymptotic level of cyanide, the level which would be reached, given sufficient equilibration time.

The problem with implementation of equation [3] for prediction of BCN is that CN produces increased $\dot{V}_E$ via

stimulation of arterial and central chemoreceptors (Way, 1984, Gonzalez et al., 1977). No quantification of the extent to which CN increases $\dot{V}_E$ is, however, available. Without consideration of the CN-increased $\dot{V}_E$, equation [3] specifies a linear increase in BCN as a function of HCN concentration in air.

If BCN were to stimulate $\dot{V}_E$ beginning at a particular level then a runaway situation would develop in which $\dot{V}_E$ would increase, followed by a further increase of BCN, followed by a subsequent increase of $\dot{V}_E$, etc., until a limiting state would be reached. The limiting state would result in an asymptotic level of BCN given a fixed HCN in air. If the increment of increased $\dot{V}_E$ were sufficiently great, the limiting state could be the maximum sustainable $\dot{V}_E$. The effect of the stimulation of $\dot{V}_E$ by BCN would be to make the uptake curve a nonlinear function of time.

Mechanism of Action

The effect of HCN on behavior and the CNS is via an inhibition of cellular respiration (cytotoxic hypoxia). This occurs because CN reacts with the trivalent iron of cytochrome oxidase in mitochondria (Way, 1984; U.S. Environmental Protection Agency, 198x). Cytochrome oxidase inhibition occurs approximately 2 min after cyanide administration (Schubert and Brill, 1968). It is also possible that CN produces effects on the CNS cholinergic and gamma-aminobutyric acid systems (Owasoyo and Iramin, 1980; Tursky and Sajter, 1962).

As CN level in the blood is increased, there is a dilation of cerebral vasculature thus supplying more blood to brain structures (Pitt et al., 1979; Klimmek et al., 1982). At

sufficiently low levels, this phenomenon seems to protect the brain against CN effects since brain oxygen consumption is not reduced for such exposures (Pitt et al., 1979). Alteration in metabolic processes by blood CN (Albaum et al., 1946; Isom et al., 1975) might also act as compensatory mechanisms (Way 1984). The persistence of each of the above compensatory mechanisms is not known. The extent of the contribution of each of the above at HCN levels less than LD_{50} is also not known.

As was mentioned in the discussion of pharmacokinetics, as blood CN increases there is a stimulation of respiration, increasing $\dot{V}_E$. Not only might that act to increase HCN intake, but hyperventilation would lower the blood level of CO_2, producing alkalosis (Lambertsen, 1980b). The alkalosis would add to any behavioral effects.

CNS and Behavioral Effects

Lethality. The lethality of cyanide is a quantitatively well described phenomenon in a wide variety of animals, humans excluded. It is not possible to describe the lethality of HCN as a constant product of time and concentration. This was extensively demonstrated by Barcroft (1931) who reported 50% lethal-concentration-time (LCt_{50}) curves for 12 species. In general, short exposures require much higher concentrations to produce lethality than do longer exposures. After 10-60 min (depending upon the species) exposure the HCN concentration required to produce lethality is relatively constant and may be considered an LD_{50}.

The sensitivity of man to HCN appears to be most similar to that of goats or monkeys (McNamara, 1976). The LCt_{50} curve for

goats published by Barcroft indicates that the lethality becomes independent of duration of exposure at ca. 30 min for goats and at ca. 45 min for monkeys. The LD_{50} for long exposures is ca. 150 and 200 ppm in monkeys and goats, respectively.

The progression of symptoms with high level HCN exposure begins with dizziness, numbness, rapid pulse, nausea, reddened skin or bloodshot eyes. These are rapidly followed by markedly labored breathing, loss of consciousness, cessation of breathing, rapid, weak heartbeat and death. Detailed descriptions of the progression of symptoms in a number of cases of accidental, nonlethal poisonings is given by Hunt (1923).

Non Lethal Behavioral Effects. In contrast to the extensive information on lethality, there are few studies on the behavioral effects of HCN exposure in the non-lethal range. Most are observational reports, not quantitative studies.

Sublethal exposures to vinyl cyanide (100 ppm) were shown to produce "lethargy and weakness" in rats, guinea pigs, rabbits, cats and dogs (Dudley et al., 1942). Hyperactivity has been reported in rats injected with 1 mg/kg of sodium cyanide (NaCN) but only qualitative observations were made (Nachman and Hartley, 1975).

Injection of NaCN in rats has been reported to impair climbing ability (or possibly recall of the task) with a 50% effective dose (ED_{50}) of 36.7 mg/kg and an LD_{50} of 131.4 mg/kg (Soine et al., 1980). An apparently linear dose-effects function was demonstrated by D'Mello (1986) in swimming escape behavior of guinea pigs after injection with NaCN. The threshold for effects

latency to begin the swimming escape appeared to be between 1.3 and 1.8 mg/kg and the effect increased approximately linearly to the highest dose given, 2.5 mg/kg. Latencies increased from control values of ca. 5 sec to ca. 18 sec at the highest dose. A required initial turning response was also affected by the NaCN. The effect was maximum about 8 min after injection and back to control values by 128 min after injection.

The only two quantitative studies found on the effects of nonlethal levels of BCN were performed on rodents and with the use of injection rather than inhalation. Considerations must be made in the interpretation of these experiments. First, rodents (especially guinea pigs) appear to differ substantially from goats and monkeys (and by inference, from man) in their LCt_{50} to CN and might therefore also differ with respect to behavioral sensitivity. Second, the use of injection avoids the irritative effects of HCN when inhaled. The irritative effects produce reduction of $\dot{V}_E$ in rodents, accompanied by a reduction in activity level (Kane et al., 1979).

With regard to the first consideration, in order to make quantitative estimates of sublethal effects from rodents to man, more data are needed on species differences in sensitivity. Even so, the linearity of the dose-effects function is likely to persist across species. As dose ranges are extended toward the LD_{50} level, it is possible that the dose-effects function will become nonlinear.

Injection of dose, as opposed to inhalation, might also make data from a rodent model more difficult to generalize to man. Man does not reduce $\dot{V}_E$ in response to irritants to nearly the

extent of rodents. However, both species will, at some level of blood CN, begin to increase $\dot{V}_E$ due to the stimulation by CN. At this time the dose of CN will be increased in a positive feedback manner. Effects of respiration might combine to make the dose effects curve nonlinear via their effect on BCN. Until much more data are available regarding the inhibition of respiration in rodents and the stimulation of respiration by CN in both species, little generalization can be made.

Electrophysiology. High level CN has been shown to affect the electroencephalogram (EEG) in a sequential manner (Ward and Wheatley, 1947). For any recording site, the normal EEG gives way to lower frequency, irregular amplitude waves, followed by near electrical silence. The cortical centers are affected first and the effect progresses caudally. During recovery, the activities return to normal in an inverse order. Such a progression is not unique to BCN, however. The EEG findings illustrate and follow the depressant effects of CN. Burrows et al. (1973) and Ashton et al. (1981) have also described the EEG effects in a more limited way. The EEG findings were extended by Purser (1984) using only 60 ppm HCN in monkeys. CNS depression was noted as well as an amplitude reduction in a late component of the auditory evoked potential. CNS depression implies an effect on behavioral alertness as well as possible other behavioral functions.

CARBON DIOXIDE (CO_2)

CO_2 is a metabolic byproduct as well as an environmental pollutant. Environmental sources of CO_2 include industrial

sources and, of course fires. The general physiologic effects of CO_2 are discussed in detail by Lambertsen (1980b).

Brain Effects

Cerebral Blood Flow and Metabolic Rate. The administration of CO_2 in inspired air produces increased cerebral blood flow (CBF) via cerebral vasodilation, resulting in a correspondingly elevated cerebral tissue partial pressure of O_2 (PO_2) which is a linear function of inhaled CO_2 (Szelenyi, 1970). The increased CBF appears to be homogeneous over grossly defined areas of the CNS (Maximilan et al., 1980; Sato et al, 1984). Similar results were found for cochlear blood flow (Hultcrantz et al, 1980) but retinal vessels were unresponsive to up to 5% CO_2 in inhaled air (Deutsch et al., 1983). Increased CBF to inspired CO_2 appears to occur independently of basal level of cerebral tissue PO_2 (Lavy and Carmon, 1969). The rise time for CBF after sudden administration of CO_2 is about 2-3 minutes and appears to be independent of CO_2 level (Shapiro et al., 1965; 1966). CBF values return to normal in about one minute after sudden return to normal inhaled air CO_2 (Shapiro et al., 1966) but large variability was reported. Newer data (Wilson et al., 1985) agree except that return to normal was longer (about 5 min).

When man is engaged in problem solving, the CBF is increased in some but not all cerebral areas (Maximilian et al., 1980). When 6% CO_2 was administered in the same study, the profiles of the CBF were the same for rest and for problem solving. Only the baseline levels of CBF were shifted up by CO_2 breathing.

The cerebral metabolic rate of O_2 ($CMRO_2$) is apparently not affected by CO_2 inhalation (Artru and Michenfelder, 1980; Barzilay et al., 1985; Dahlgren et al., 1981; Hoffman et al., 1982; Kassell et al., 1981; Shapiro et al., 1966) sufficient to produce even extreme hypercapnia, despite an earlier report of decreased $CMRO_2$ (Kliefoth et al., 1979). Thus, even though available O_2 (Szelenyi, 1970) is increased by CO_2 inhalation via CBF increases, the cerebral utilization of O_2 remains constant and appropriate to demand (Dahlgren et al., 1981). This conclusion probably holds for all levels of cerebral tissue PO_2 from normoxia and well above.

Electrophysiology. Inhalation of ca. 5% CO_2 produces EEG signs which may be interpreted as arousal (Gibbs et al., 1940; Harter, 1967; Ivanov, 1962; Lansing and Crown, 1969; Lavy and Carmon, 1969; Lavy and Tiberin, 1964; Mattsson et al., 1972). Levels greater than about 6%, however produce EEG signs which are similar to early anesthesia (Gellhorn and Hailman, 1944; Harter, 1967; Mattsson et al., 1972). Auditory evoked potentials were slightly increased in latency by 5% CO_2 (Deecke et al., 1973) but the brainstem auditory evoked response was unaffected even by 10% CO_2 (Sohmer et al., 1982).

The excitability of single cells in the CNS follows a similar pattern to the EEG. Below 5% inhaled CO_2, the effect was excitatory but at 5% and above the effect becomes depressant (Krnjevic et al., 1965; Morris, 1969). There was no effect of 5% CO_2 on the electroretinogram (ERG) but at 10% CO_2 the ERG amplitude was depressed (Niemeyer et al., 1982).

Apparently the single cell effects, and perhaps the effects of CO_2 on the EEG are not mediated by the increased CBF. In isolated cortical slabs, CO_2 administration did not produce increased CBF but did affect electrical activity (Soderberg, 1964). That the CBF autoregulatory mechanism was still intact, however, was demonstrated by the fact that CBF still increased with increased electrical activity.

Effects on Respiration

A description of the interoceptive and respiratory effects of CO_2 in man is given by Lambertsen (1980b). Below 3% CO_2 in inspired air, no effects are noticed. At 4% and above, respiratory stimulation proportional to the CO_2 level occurs, accompanied by generalized arousal. Dyspnea begins to occur between 7 and 10%. Very high levels (ca. 30%) of CO_2 produce immediate panic responses in subjects (Van Den Hout and Griez, 1985). Continued inhalation of CO_2 levels between 7 and 10% will produce progressively worsening symptoms of listlessness, dyspnea, faintness and severe headache. Between 15 and 20% muscular tremors and rigidity occur and between 10 and 30% generalized seizures occur in a short time.

Figure 3, depicts the mean respiratory response to CO_2. little or no response occurs below about 3% CO_2 in the average curve. Even though the ventilatory response to inspiration of CO_2 is quite stable for a given subject (Singh, 1984), there is a large variability across individuals and states of alertness (Lambertsen, 1960). Thus the curve of Figure 3 must be interpreted with caution in the case of the individual.

Insert Figure 3 about here.

The respiratory response to CO_2 inhalation can be partially overridden for long periods of time by voluntary behaviors such as speaking (Phillipson et al., 1978), by hypnotic suggestion (Sato et al., 1986) and possibly by training (Florio et al., 1979). The ventilatory response to CO_2 was reduced by hypothermia (Ruiz, 1975) and by sleep deprivation (Sato et al., 1986).

Task Performance.

With various O_2 levels from 21-50% and CO_2 levels up to 5% there were no effects of CO_2 on simple or choice reaction time, short term memory, reasoning tests or pursuit rotor performance either while human subjects were at rest or exercising at 80% of maximum aerobic capacity (Sheehy et al., 1982). Using only two human subjects breathing 50% CO_2 in air, there were no effects on a motion compensation task but a simulated aircraft landing task was possibly slightly affected (Wamsley et al., 1969). Serial choice reaction time was increased in highly practiced young men by administration of 4% CO_2 in room air (Vercruyssen, 1984). Sleep stages were disturbed in rats when CO_2 level exceeded 5% (Ioffe et al., 1984). Arithmetic and reaction time performance was decremented by 5% CO_2, but tracking was not (Schaad et al., 1986). Inhalation of up to 4% CO_2 reduces auditory sensitivity (Gellhorn and Spiesman, 1935) and pain sensitivity (Stokes et al., 1948).

Apparently the effects of CO_2 administration up to 4 - 5% have no effect and become harmful for higher levels. The exact level at which CO_2 begins to affect performance in any given subject is likely to vary widely, as does the respiratory response. There are no data on this possibility, however. Similarly, the behavioral decrement might be a function of such variables as the subject's training under similar circumstances and the nature of the task itself.

Not much dose-effects information exists for the behavioral effects of CO_2, but it is clear that the effects do not occur to an appreciable extent until about 4 - 5% levels. It is likely that above the 5% level of CO_2, the dose-effects function continues to rise and form the seemingly ubiquitous positively accelerated function of dose until the limiting effects of seizures occur.

HYPOXIC HYPOXIA

The lack of O_2 in the inspired air (hypoxic hypoxia) is one of the conditions resulting from fires. The normal percentage of O_2 in air is 21%. The extent of hypoxia is usually expressed as the concentration of O_2 in percent. It is also sometimes convenient to express hypoxia as percent of O_2 below normal.

Data regarding the effects of hypoxia were frequently gathered because of interest in the hypoxic effects of high altitude. The results obtained in altitude chambers can be compared to those obtained by simple O_2 reduction by conversion of altitude to equivalent percent O_2. Figure 4 is a nomogram for conversion of altitude (in either ft or m) to equivalent percent

Another effect of increasing hypoxia is a corresponding increase in cerebral vasodilation and consequently increased CBF (Traystman et al., 1978). This compensatory response continues from 21% O_2 down to as low as 4% O_2 in anesthetized dogs and is similar to that produced by elevated COHb.

Behavioral Effects

There is considerably agreement among investigators about effects of hypoxic hypoxia. This is probably because wide range dose-effects functions have been the usual product of research rather than point estimates of effects thresholds, as in CO experiments. Interest in wide range dose-effects functions was the natural product of the fact that man has historically attempted to extend the tolerance of the lower limit of O_2.

The following review concentrates upon the dose-effects relations which can be found in the literature. A less thorough review of other effects is given. For more details regarding other effects, see Tune (1964).

Sensory. The visual system seems to be most readily affected by hypoxic hypoxia (Tune, 1964). Dark adapted absolute visual thresholds were raised beginning with O_2 levels of ca. 15% and increasing in a dose-related fashion until the most hypoxic group at 11% O_2 (McFarland et al. 1941). Dark adaptation effects were not homogenous for rods and cones and for peripheral rods and foveal rods (Ernest and Krill, 1971). Luminance thresholds for non- laboratory type stimuli (persons, vehicles, etc.) were increased in a 12% O_2 atmosphere, but the effect was not at maximum until the 2nd day of continued exposure after which

decrements began to ameliorate (Kobrick, 1983).

The reaction time for the detection of peripheral visual stimuli was increased by exposure to hypoxia ranging from 13 - 11% inspired O_2 (Kobrick and Dusek, 1970; Kobrick, 1975). The maximum effect did not occur until ca. 90 min of exposure, however, after which there was an amelioration. The two studies were conducted at luminances typical of daytime as well as nighttime viewing. It is not clear what the increased reaction time implies, but because reaction time also increase as the stimulus is presented more peripherally, it is logical that the effect is upon visual processes and not simply a reaction time phenomenon.

The duration of the afterimage following visual stimulation was increased by levels in atmospheres ranging from 13 - 10% O_2 in a dose-related manner (McFarland et al., 1941). Although 13% was the highest O_2 level, other than control, it appears from the curves that the threshold for effects would be about 15 - 14% O_2. In the same study, it was also shown that 10% O_2 reduces foveal visual acuity. The color field is decreased in size by O_2 levels of ca. 12% and lower (Vollmer et al., 1946, Kobrick, 1970). From the graphs presented in his study, it appears that the effects might occur for less extreme hypoxia.

Vigilance. Vigilance was decremented in a dose-related manner by exposure to atmospheres of 13 - 11% O_2, using either visual or auditory signals (Cahoon, 1970, 1973). Fiorica et al., (1971) failed to find significant effects at 13.1% o_2 but the task used was probably not as demanding as that of Cahoon. O'Hanlon and Horvath (1973) observed a vigilance decrement with

11.4% inspired O_2 and using the same task, Christensen et al. (1977) reported a vigilance decrement even at 17% O_2.

Psychomotor. Postural stability is reduced during exposure to 11.4% o_2 (Vollmer et al., 1946) and slightly at ca. 16% O_2 (Holness et al., 1982). Slight effects were noted on complex compensatory tracking at ca. 11% O_2 (Figarola and Billings, 1966). Without further psychomotor data, little can be said regarding thresholds or dose-effects functions.

Cognitive and reaction times. Logical reasoning task performance was decremented in atmospheres of 12.8% O_2 but not at 14% O_2 (Green and Morgan, 1985). An atmosphere of 15.4% O_2 had no effect on card sorting (Kelman et al., 1969). Similarly, at 14.5% O_2, Innes and Allnutt (1967) found no effects on a wide variety of cognitive and perceptual task performance, despite anticonservative statistical procedures. Mannekin rotation problem solving was affected only temporarily by 17.4 and 15.2% O_2 (Denison et al., 1966). Effects on choice reaction time and movement time were affected in a non-dose-ordinal manner by atmospheres of 16 and 14.3% O_2 (Ledwith, 1970).

Summary. Visual effects of hypoxia are consistent and well documented by comparison to the effects of COHb. The effects of Hypoxic hypoxia on vigilance seem also to be systematic and well documented. Not much seems to have changed since a review (Tune,1964) with respect to other behavioral or sensory functions. Studies of other dependent variables are mostly illustrative of effects at one or a few levels of hypoxia. Because of major differences across experiments in tests

employed, no coherent pattern emerges. It does appear that some cognitive behaviors are affected by hypoxia at thresholds in the vicinity of those for visual and vigilance effects.

Figure 6 is a plot of data from McFarland et al. (1944), Cahoon (1973) and Kobrick (1975). The points are their published means. The curves, as has been true for previous toxicants, are nonlinear positively accelerated functions. Because blood alkalosis does not begin to develop until 12 - 10% O_2 in inspired air, it would appear from Figure 6 that much of the the hypoxia dose-effects function is due to reduced O_2 delivery, not the alkalosis due to hyperventilation. Effects are already obvious by the time alkalosis develops.

Insert Figure 6 about here.

REVIEW OF EFFECTS OF COMBINATIONS OF INHALED SUBSTANCES CARBON DIOXIDE AND HYPOXIC HYPOXIA

The effects of combined exposure to CO_2 and hypoxic hypoxia are well documented. During hypoxic hypoxia the PO_2 of arterial blood drops, $\dot{V}_E$ increases and, as a consequence, arterial PCO_2 is decreased below normal. Blood alkalosis results from the reduced PCO_2. Addition of small amounts of CO_2 to the inhaled hypoxic air (a) elevates the blood PCO_2, reducing the alkalosis, (b) further stimulates $\dot{V}_E$, thus increasing blood PO_2 and (c) produces further increases in CBF. More detail is found in Lambertsen (1980a). Thus the general effect of adding small amounts of CO_2 to hypoxic air is to attenuate the physiological effects of hypoxia.

Administration of up to 5% CO_2 reduces the effects of hypoxic hypoxia on memory and cognitive function (Gellhorn, 1937). Similar results are found in rhesus monkeys (Karl *et al.*, 1978). Visual intensity discrimination which had been decremented by hypoxia was restored by administration of 3% CO_2 (Gellhorn, 1936). When EEG is slowed by hypoxia addition of CO_2 (3-5%), ameliorates the effect (Gellhorn and Hailman, 1944; Rebuck *et al.*, 1976).

CARBON MONOXIDE AND HYDROGEN CYANIDE

Both elevated COHb and HCN are assumed to produce their effects via hypoxia at the tissue level. COHb elevation reduces the ability of the blood to carry O_2 while HCN inhibits tissue respiration. Both of the substances also produce increased CBF. HCN also produces increased $\dot{V}_E$. The increased CBF apparently acts as a compensatory mechanism at low levels of exposure, ameliorating CNS and behavioral effects by supplying more volume of blood and thus more O_2.

Pitt *et al.* (1979) measured both CBF and brain O_2 consumption in dogs with various blood levels of CN and COHb. As expected, both CN and COHb elevated CBF. When both COHb and CN were present, the CBF was increased additively. The brain O_2 consumption was not affected at lower levels of either CN or COHb (1 microgram/ml of CN and 30% COHb). When the two lower levels of COHb and CN were combined, however, brain O_2 consumption decreased. Thus, while the effects of the two substances were additive over a wide range for CBF effects, they were synergistic for effects on brain O_2 consumption.

The effect on lethality of COHb and CN in combination have been tested in rats by a number of investigators. Moss et al. (1951) reported apparently synergistic effects but their documentation was not detailed and they apparently used only a few rats which exhibited great variability. Norris et al. (1986) administered CO by inhalation and produced high blood CN levels by injecting potassium cyanide. They reported synergistic effects. In contrast, Levin et al. (1987) found only additive effects when CO and HCN were administered by inhalation. Perhaps the critical variable which differed between the studies was the method of producing blood CN. Since blood CN was not reported by Levin et al. (1987) it is not possible to evaluate the hypothesis.

From the above meager data it is not unreasonable to assume that at low levels of COHb and CN the effects might be additive. At lethal levels, there is reason to believe that synergistic effects might occur but the data are not clear. Perhaps some variables are affected additively while others are affected synergistically (Pitt et al., 1979). It is also possible that the effects observed on lethality and incapacitation might not be representative of effects due to lower-level exposures.

CARBON MONOXIDE AND HYPOXIC HYPOXIA

Both CO and hypoxic hypoxia result in reduced O_2 supply to tissue. Both COHb elevation and hypoxic hypoxia produce increased CBF, the latter probably tending to offset tissue hypoxia. Hypoxic hypoxia also produces increased $\dot{V}_E$, which increases blood PO_2 but also produces alkalosis. Thus it would appear that effects of the two together might produce a more

extreme increase in CBF and simply compensate for the decreased O_2 content of arterial blood and thereby prevent behavioral effects. At some point, however the arterial blood O_2 will drop sufficiently so that effects must occur.

Vollmer et al. (1946) tested human subjects exposed to 11.4 or 14.0% O_2, either alone or in combination with up to 20% COHb. Tests of color field extent, critical flicker fusion and postural stability were affected by hypoxic hypoxia but no additional decrement was produced by COHb. The authors hypothesized that cardiorespiratory compensatory mechanism prevented added COHb effects. More recently a 17% O_2 atmosphere was shown to produce a small vigilance decrement but when ca. 5% COHb was developed, the effects seen in hypoxic hypoxia were eliminated (Christensen et al., 1977). The authors also invoked compensatory mechanisms as a possible explanation, but both the hypoxic and COHb levels were so low that the normal variance might well have masked small effects. Using mice in a pole-jump avoidance task, Cagliostro and Islas (1983) demonstrated two dose-effects functions for hypoxia, one with and one without ca. 17% COHb. The function for hypoxia plus COHb was shifted to the left to an extent that implied a synergistic effect. The pole-jump task involves physical exercise and is a strongly-motivated escape behavior. The imperative work might have created a competition for O_2 supply with the brain or might have affected musculature.

A PREDICTION MODEL FOR COMBINATIONS OF THE TOXIC GASSES

The effects of each of the toxicants in question are, by no means simple and, in most instances, much uncertainty about actual effects remains. In the case of CO the literature is

badly confused concerning the neurobehavioral effects. Little information exists concerning behavioral effects of cyanide below lethal levels. Behavioral effects of CO_2 above 5% are lacking.

Effects of combinations of two toxicants become more complex, involving a number of provisos and interrelated physiological events. When all four of the substances are combined, the level of complexity becomes unwieldy at very best. Symbolic statement of the effects can be used to encode the present knowledge into quantitative forms. Such forms can be used to make theory explicit and to generate specific predictions (supposing the coefficients of the forms can be specified). Even without specific coefficients, the shape of multiple-toxicant dose-effects curves can be predicted via simulation. It is probable that without mathematical encoding of knowledge, specific predictions could not be made.

GENERAL CONSIDERATIONS

Forms for Individual Toxicants.

The behavioral dose-effects curve for each of the substances considered in the above review was a nonlinear, positively accelerated function, except for HCN, for which not enough data were available. Even the dose-effects functions for the effects of CO_2 and hypoxia on $\dot{V}_E$ were positively accelerated.

The particular form of the function cannot be specified without a great amount of raw data analysis. In lieu of an objectively selected model, a first approximation form has been selected because of its reasonable shape and parsimony. The model is the same as used in Benignus *et al.* (1988b) to describe

COHb effects. Figure 2 shows the form as fitted to COHb data from various sources. The form is

$$E(X_{ij}) = \beta(X_j)^2 + e_{ij} \qquad [4]$$

in which;

$E(X_{ij})$ = behavioral effect for substance X at level j, on subject i

X_j = the body burden of substance X

β = an empirical coefficient describing the slope of the curve.

e_{ij} = a normally distributed random variable representing the variability of measurement on subject i for substance X at level j.

Since the form used in equation [4] was not empirically determined to be optimum for any case, it must be regarded as a plausible stand-in until better analyses can be made. It must also be pointed out that the form might not fit well in some cases. This is not known since empirical fits have not been tried. Furthermore, at some point the phenomenon described by equation [4] will reach a limiting state. The equation does not describe such a state and as higher levels are approached, the equation is bound to become inappropriate. The form is only a plausible positively accelerated equation selected to work over a limited, lower range.

Because the dose-effects curves so uniformly were positively accelerated functions, it is not unreasonable to suppose that that form would also eventuate for HCN. Granted, there are also reasons to suppose that such a form would not apply. In the absence of more data, and because of the pervasiveness of the

nonlinearity, the form of equation [4] will also be provisionally adopted for HCN.

Especially in the effects of CO_2 on $\dot{V}_E$, there were substantial individual differences in sensitivity. These would translate into differences among subjects in the value of the term "β" in equation [4], the slope of the curve. If the sensitivity of the subject were known (from, e.g. previous measurement) some of the variability could be accounted for by selecting a unique value for β for each subject. In that case the term would be subscripted as (β_i).

In equation [4] the level of substance (or condition) X is to be specified as given in Table 2. Values for CO and HCN are blood levels, not environmental air levels. The reason for that strategy is to be able to calculate the effective amount of a substance that is acting in the body. Given a fixed environmental level, blood levels might vary widely due to physiological effects of stress, exercise and other co-toxicants.

Insert Table 2 about here.

The measurement of hypoxia deserves special comment. Usually hypoxia is specified as the percent O_2 in inhaled air. This results in an inverse horizontal scale for the dose-effects plot (see Figures 5 and 6) or a graph in which effects rise toward the left of the graph. To avoid this inconvenience in mathematical models, hypoxia was specified as a reduction in O_2 in inhaled air. The reduction in O_2 in inhaled air is expressed

as the level of hypoxia by

$$HYP = 21 - (\text{reduced } O_2) \qquad [5]$$

in which

HYP = the measurement of hypoxia as reduction in O_2 from normal (21%) by the O_2 level in hypoxic air.

Minute Ventilation Effects.

Both CO and HCN are absorbed via pulmonary ventilation at a rate determined in part by $\dot{V}_E$ (see equations [1 and 3]. $\dot{V}_E$ is determined by, among other things, the level of CO_2 inhalation (see Figure 3), the level of hypoxic hypoxia (see Figure 5) and the level of HCN inhaled. In the case of HCN, no parametric data are available on the levels of HCN vs. $\dot{V}_E$. If blood levels of CO and CN are to be estimated, $\dot{V}_E$ must be estimated.

It is reasonable to assume that the effects on $\dot{V}_E$ of CO_2, hypoxic hypoxia and HCN are additive in the range of exposure below which $\dot{V}_E$ can still increase. If this is the case then $\dot{V}_E$ can be estimated by

$$\dot{V}_{E_{ijkm}} = \dot{V}_E(B_i) + f(^{CO_2}{}_j) + f(HYP_k) + f(HCN_m) \qquad [6]$$

in which

$\dot{V}_{E_{ijkm}}$ = the minute ventilation of subject i at CO^2 level j, Hypoxia level k and HCN level m,

$\dot{V}_E(B_i)$ = observed baseline pulmonary ventilation of subject i without additional influences,

$f(^{CO_2}{}_j)$, $f(HYP_k)$ and $f(HCN_m)$ are equations specified below. Because the stimulation of $\dot{V}_E$ by CO_2 and by hypoxia follows the familiar positively-accelerated function (for lower levels of CO_2), it is probable that the form used in equation [4] would

fit. It is also likely that the CN stimulation of $\dot{V}_E$ follows the same function. Accordingly, that function is provisionally adopted for $f(^{CO}2_j)$, $f(HYP_k)$ and $f(HCN_m)$.

The relative importance of Hypoxic hypoxia with respect to CO_2 in the determination of $\dot{V}_E$ is probably small in most instances. Comparison of Figures 3 and 5 reveals that CO_2 is a much more powerful respiratory stimulant in the range of interest than is hypoxia hypoxia. Note that COHb elevation does not affect pulmonary ventilation as do the other three substances.

Given levels of CO_2, hypoxia and HCN, their contribution to $\dot{V}_E$ can be estimated as $\dot{V}_{E_{ijkm}}$ via equation [6]. When a pharmacokinetic equation calls for $\dot{V}_E$, the above value would be entered for a subject at rest. If a subject is exercising, is subjected to high temperatures or to stress, those effects on $\dot{V}_E$ would be determined first to produce $\dot{V}_E(B_i)$ in equation [6].

EFFECTS OF COMBINATIONS OF SUBSTANCES

Additivity and Synergism.

On an empirical level, too few data are available to decide whether the above toxicants might produce additive effects in combination or whether their effects might be synergistic. For purposes of model construction, it was decided to use additive combinations. At the present stage of construction, any model must be considered to be provisional anyway. Should it become reasonable, on empirical grounds, non-additive terms can be added as e.g. scaled multiplicative combinations of simple effects.

A Combined-Exposure Model.

To employ a model to predict the effects of combined toxicant exposure as proposed below, one must have had to first estimate blood levels of the toxicants and blood gasses via pharmacokinetic equations. The pharmacokinetic equations which require $\dot{V}_E$ will have necessitated use of equation [6] to make the estimate. After blood level estimates have been made, equations of the form [4] can be used to estimate the individual substances or condition's effect on the behavior in question. Following this, and allowing the additive assumption

$$E(C)_{ijkmn} = E(COHb)_{ij} + E(BCN)_{ik} + E(CO_2)_{im} + E(HYP)_{in} \quad [7]$$

may be used to estimate the combined effect. In the above

$E(C)_{ijkmn}$ = The behavioral effect of the combination of exposures at levels j,k,m and n on subject i,

$E(COHb)_{ij}$ = effect of COHb at level j on subject i,

with the remaining terms defined similarly.

Equation [7] is identical to the additive model published by Purser (1986). The differences between the present modeling procedure and the one by Purser lie in (a) the dependent variables predicted by the individual models comprising equation [7] and the consequent curve shape for the dose-effects function (b) the basing of dose measurements on blood levels rather than (in most cases) atmospheric levels and (c) the more extensive specification of effects on $\dot{V}_E$ by the various substances and conditions.

It appears from equation [7] that the relationship between the various effects is additive. That is somewhat of an oversimplification, however. It would be more accurate to say

that after the complex physiological and pharmacokinetic interactions have been mathematically accounted for, the behavioral effects are hypothesized to be additive.

DISCUSSION AND CONCLUSIONS

A series of summary statements may be made about the effects of the substances and conditions. These statements are most conveniently made with reference to the model which has been defined.

SUMMARY POINTS

(1) Dose-effects graphs for all of the substances and conditions are probably nonlinear, positively accelerated functions below some upper limit range. It was proposed that equation [4] be used to model the curves.

(2) For CO and HCN it was proposed that COHb and BCN be used as dose measures instead of atmospheric levels. These are descriptors of body burden of the toxicant and appear as X_j in equation [4]. Use of the atmospheric levels permits too much variability due to the effects of the toxicants and conditions on uptake into the blood.

(3) Estimation of COHb and BCN by use of pharmacokinetic equations [1 and 3] requires the estimation of $\dot{V}_E$. Estimation of $\dot{V}_E$ requires estimation of the effects of HCN, CO_2 and HYP on $\dot{V}_E$ via equation [5].

(4) At lower levels, HYP does not appreciably affect $\dot{V}_E$. The stimulatory effect of HCN has not been quantitatively described. CO_2 probably is the most important stimulus to increased $\dot{V}_E$.

(5) Having estimated $\dot{V}_E$ via equation [5] and then COHb and BCN via equations [1 and 3], behavioral effects of the individual toxicants or conditions can be estimated via equations of the form of [4].

(6) The assumption was made that the behavioral effects of the individual toxicants or conditions would be additive. The following points justify the strategy of the additive assumption.

(a) CO, HCN and HYP all have as their principal mechanism of action, the reduction of O_2 supply to tissue.

(b) Empirically, each of the substances and conditions has a depressant effect on the CNS at lower levels of stimulation.

(c) Little evidence of non additive effects was found in a literature review of effects of simultaneous exposure to binary combinations of substances or conditions.

(d) Until hard evidence of synergistic effects at exposure levels below incapacitation or lethality becomes available, considerations of parsimony dictate selection of additive models.

(7) The model is provisional and awaits data before certain relationships and effects of single substances or conditions can be specified.

(a) A wide range dose effects function is not available for the behavioral effects of HCN

(b) A pharmacokinetic equation for HCN has not been fully developed, although a beginning has been made in this

chapter.

(c) Wide range behavioral dose effects functions have not been developed in humans for COHb and BCN. There are also no theoretical or empirical ways to quantitatively infer such functions from laboratory animal data.

(d) Raw data must be used to fit particular functions so that quantitative predictions may be made from the model. At present, only the forms of the relationships have been hypothesized. The equations for the dose-effects functions are likely to change when such fitting is attempted.

(8) Almost no systematic data regarding the behavioral effects of exposure to multiple substances or conditions are extant. Understanding effects of simultaneous multiple exposures via an empirical research program would require construction of families of dose-effects functions. Such a process is so time consuming that it is unlikely to be undertaken.

(9) After enough work is done to find best fit forms for the equations and values for empirical coefficients, experimental "spot" testing of the predictions of the model for combinations exposures would allow a self-correcting series of studies to be performed until predictions were correctly generated. After this, confidence in model predictions would be sufficiently high to allow the use of less expensive simulations to predict the families of dose-effects functions.

(10) Without a model to generate predictions, the problem of

multiple-substance exposure is unlikely to be soluble in general. The possible combinations of events and levels of exposure are too manifold. The best that can be hoped for in the absence of a good model is a set of special cases, each one peculiar to the purpose for which it was derived.

EXPOSURE SAFETY GUIDELINES

In view of the above review and discussion it seems presumptuous to consider quantitative guidelines for exposure safety. This is especially true for HCN. Nonetheless, some information can be systematically presented and, not without risk, be given as guidelines. No applied tasks will be cited. Instead, laboratory tasks will be given and the user must decide how and to what extent the tasks are typical of whatever applied behavior is in question.

Single Substance Exposure

Table 3 gives two levels of exposure which may be considered by persons concerned with exposure assessment and/or control. The first, "lowest effect level" is the lowest level reported to have been effective in producing detrimental effects. Such a value is especially sensitive to Type I errors. The second level, "frank effects level", is the lowest exposure level which was reported to be unambiguously above threshold in a dose-effects function or has been consistently reported to produce effects. Due to lack of information, the table must be interpreted by the user. If the primary concern is upon safety from exposure or small effects in critical tasks, thelowest effect level, or perhaps even lower, should be used. If applications are to less critical tasks or emergency conditions obtain, higher levels

might be appropriate. Too little data are available to make the data cited in Table 3 more than of interim value.

Multiple Substance Exposure

Even though it was hypothesized above that the effects of individual substance exposure were additive when combination exposures occurred, no quantitative data are available for determining the weighting coefficients for each effect. Furthermore, unless the effects of pulmonary stimulation by CO_2, cyanide and hypoxic hypoxia can be properly assessed, the pharmacokinetics of multiple substance exposure cannot be evaluated. Any guidance given here would almost surely, therefore be in error. The best guide is previous experience in similar situations. Perhaps the best answer for the general case lies in research directed toward general understanding so that particular coefficients can be determined for models similar to the one proposed in this chapter.

TABLE 1

COMPONENTS OF FIRE PRODUCTS AND CONDITIONS TO BE CONSIDERED IN THE PRESENT CHAPTER

SUBSTANCE/ CONDITION	SUPPOSED MECHANISM OF CNS OR BEHAVIORAL EFFECT
CO	production of hypoxia via reduction of O_2-carrying capacity of the blood
HCN	production of hypoxia by interference with cellular respiration
Hypoxic hypoxia	hypoxia by reduction of available O_2
CO_2	small CNS effects - elevates pulmonary ventilation
Irritants	broad category of substances which interfere with performance by generating competing responses e.g. aldehydes, hydrochloric acid, phosgene and ammonia to mention but a few.

TABLE 2

MEASUREMENT UNITS FOR THE SUBSTANCES OR CONDITIONS TO BE USED IN EQUATION [4]

SUBSTANCE/ CONDITION	MEASUREMENT UNIT
CO	Percent carboxyhemoglobin (COHb) saturation
HCN	Blood cyanide level, mg/kg
CO_2	Percent CO_2 in inspired air
Hypoxic hypoxia	[1]Reduction of O_2 in inspired air in %

[1]Normal concentration of O_2 is 21%. Reduction in O_2 is to be specified as the difference of the concentration from normal in %.

TABLE 3

EFFECTS OF EXPOSURE TO SINGLE

SUBSTANCES OR CONDITIONS

SUBSTANCE/ CONDITION	LOWEST EFFECT LEVEL	FRANK EFFECT LEVEL	NOTES
COHb	5%	>20%	Frank effects level was extrapolated for man from dose-effects curve in Benignus et al. (1988b). Much remaining conflict in literature. hand-eye coordination and possibly vision and vigilance appear affected.
Cyanide	1.3 mg/kg	?	Studied only in rat. Few studies. Effects were on maze performance and motor coordination.
Hypoxic hypoxia	16% O_2	12% O_2	Affects visual processes, vigilance and possibly motor and cognitive function. Lowest reported effect was very slight in one study.
CO_2	4%	>5%	Effects above 5% poorly documented. Effects were on respiration, many aspects of performance - motor, sensory and cognitive.

FIGURE CAPTIONS

Figure 1. COHb as a function of time for a fixed atmospheric CO concentration (200 ppm) and for two levels of V_A. Curves were generated by computer using the model of Coburn et al. (1965), assuming sea level exposure, 15 g of Hb per 100 ml of blood and Haldane constant of 760.

Figure 2. Dose effects functions from various studies of COHb effects in rats and man. Dotted line above 20% COHb for human data represents extrapolation. Reprinted from Benignus et al. (1988b).

Figure 3. Effect of CO_2 on $\dot{V}_E$. Curve was constructed from group mean data published by Lambertsen (1960).

Figure 4. Nomograph for conversion of altitude to equivalent O_2 concentration in air.

Figure 5. Effect of O_2 deficit on $\dot{V}_E$. Constructed from data published by Dripps and Comroe (1947).

Figure 6. Effects of hypoxic hypoxia on various visual tests and vigilance. Data for McFarland et al. were obtained by averaging the last five values in their dark adaptation curves in their Figure 1. Data for Kobrick were read directly from his Figure 3 for the 12^{o} stimuli reaction times. Data for Cahoon were read directly from his Figure 1. All data were converted to the same scale using procedures given in Benignus et al. (1988b).

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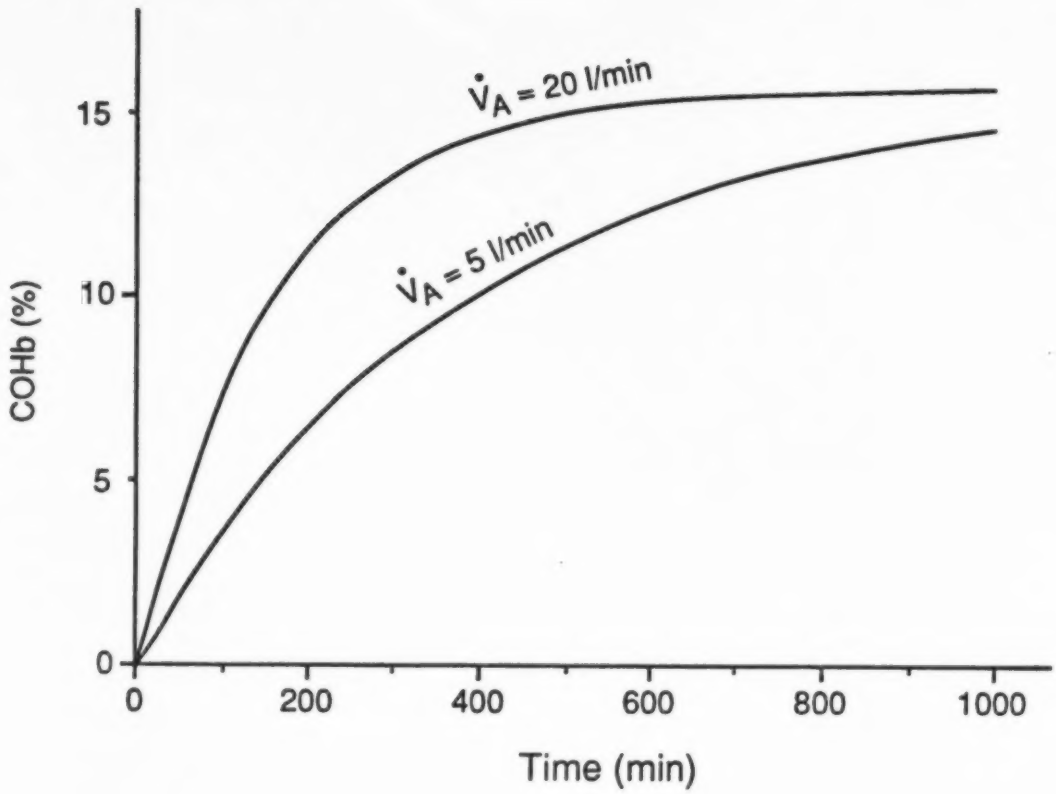

Figure 1. COHb as a function of time for a fixed atmospheric CO concentration (200 ppm) and for two levels of $\dot{V}_A$. Curves were generated by computer using the model of Coburn et al. (1965), assuming sea level exposure, 15 g of Hb per 100 ml of blood and Haldane constant of 760.

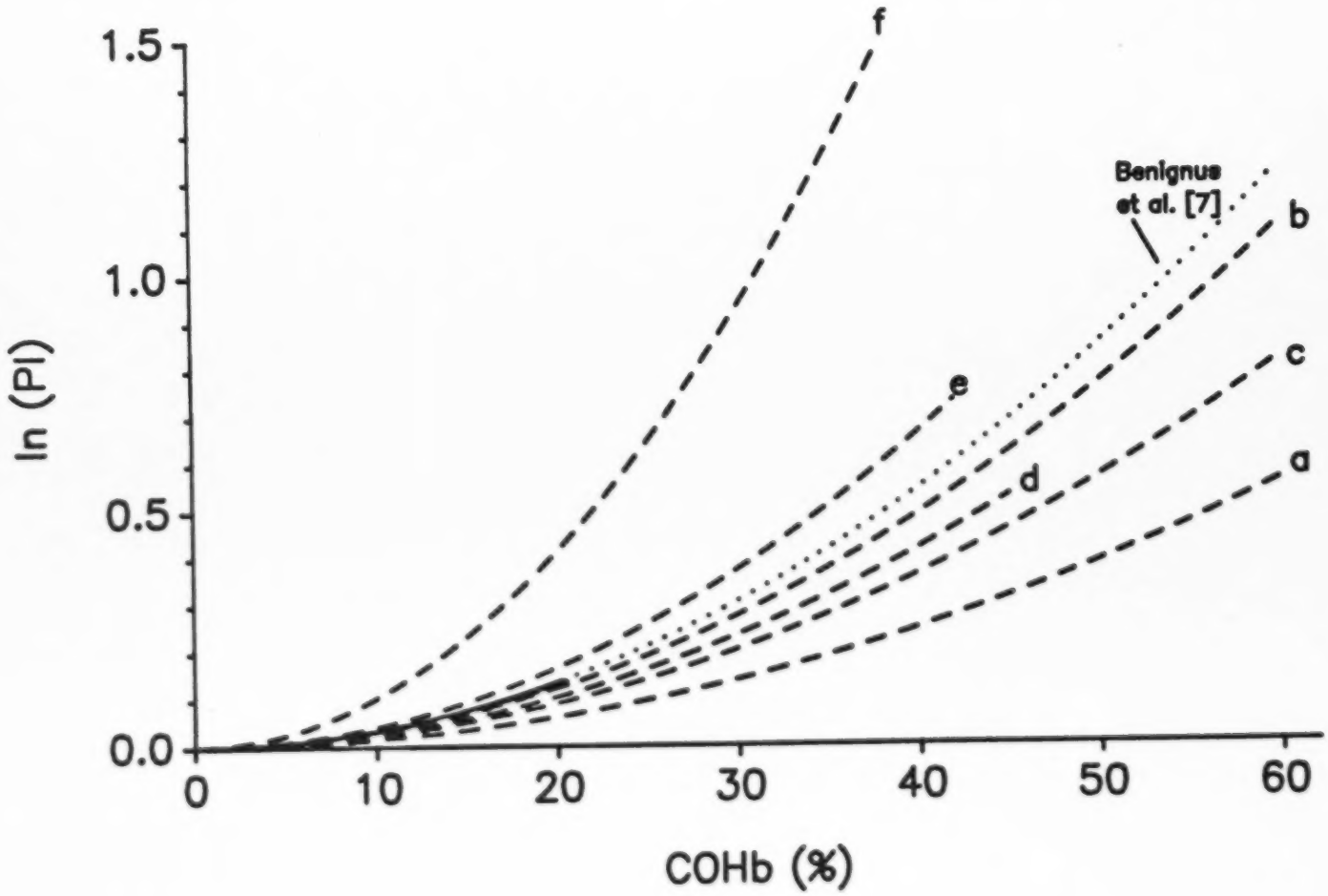

Figure 2. Dose effects functions from various studies of COHb effects in rats and man. Dotted line above 20% COHb for human data represents extrapolation. Reprinted from Benignus et al. (1988b).

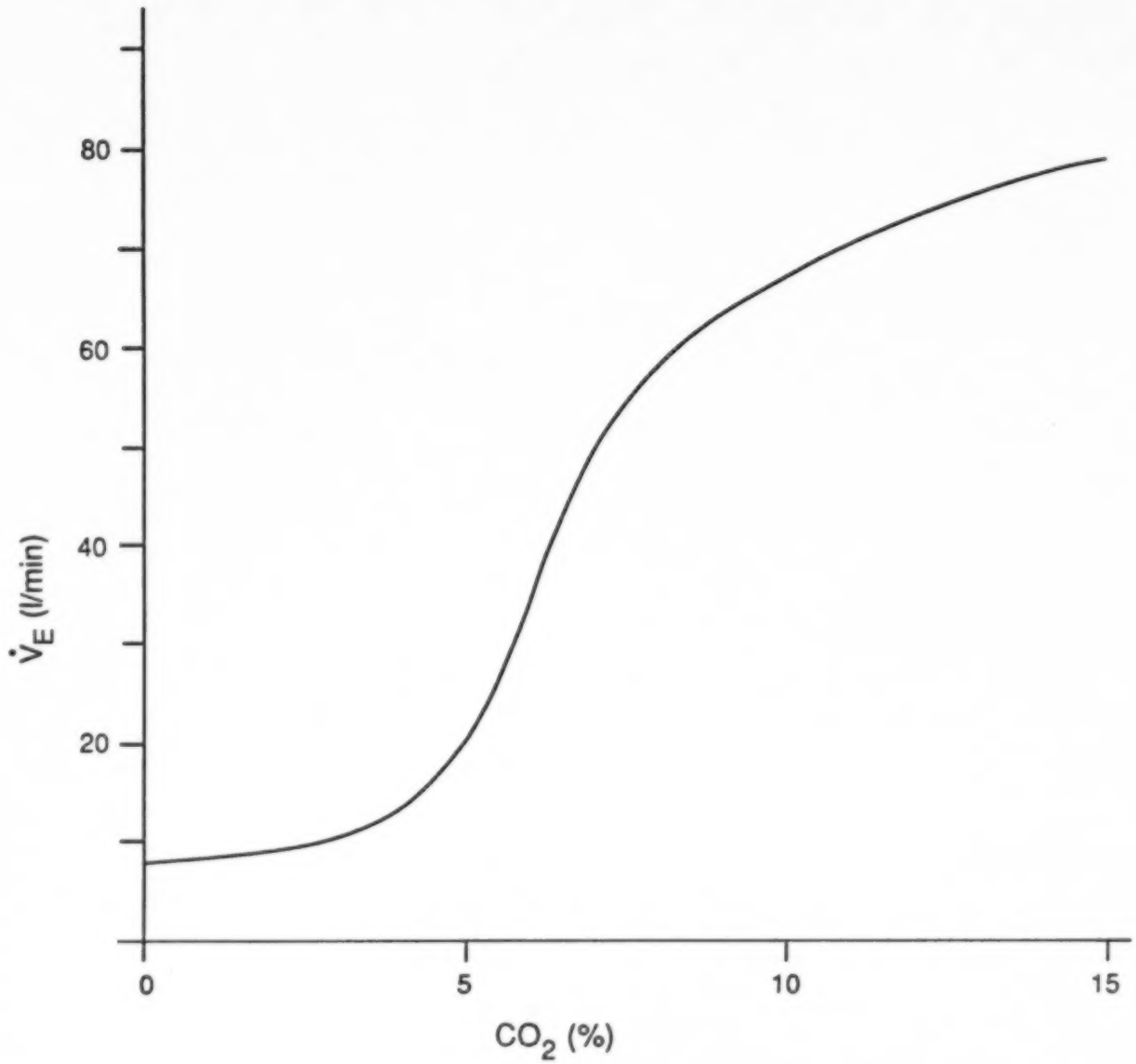

Figure 3. Effect of CO_2 on $\dot{V}_E$. Curve was constructed from group mean data published by Lambertsen (1960).

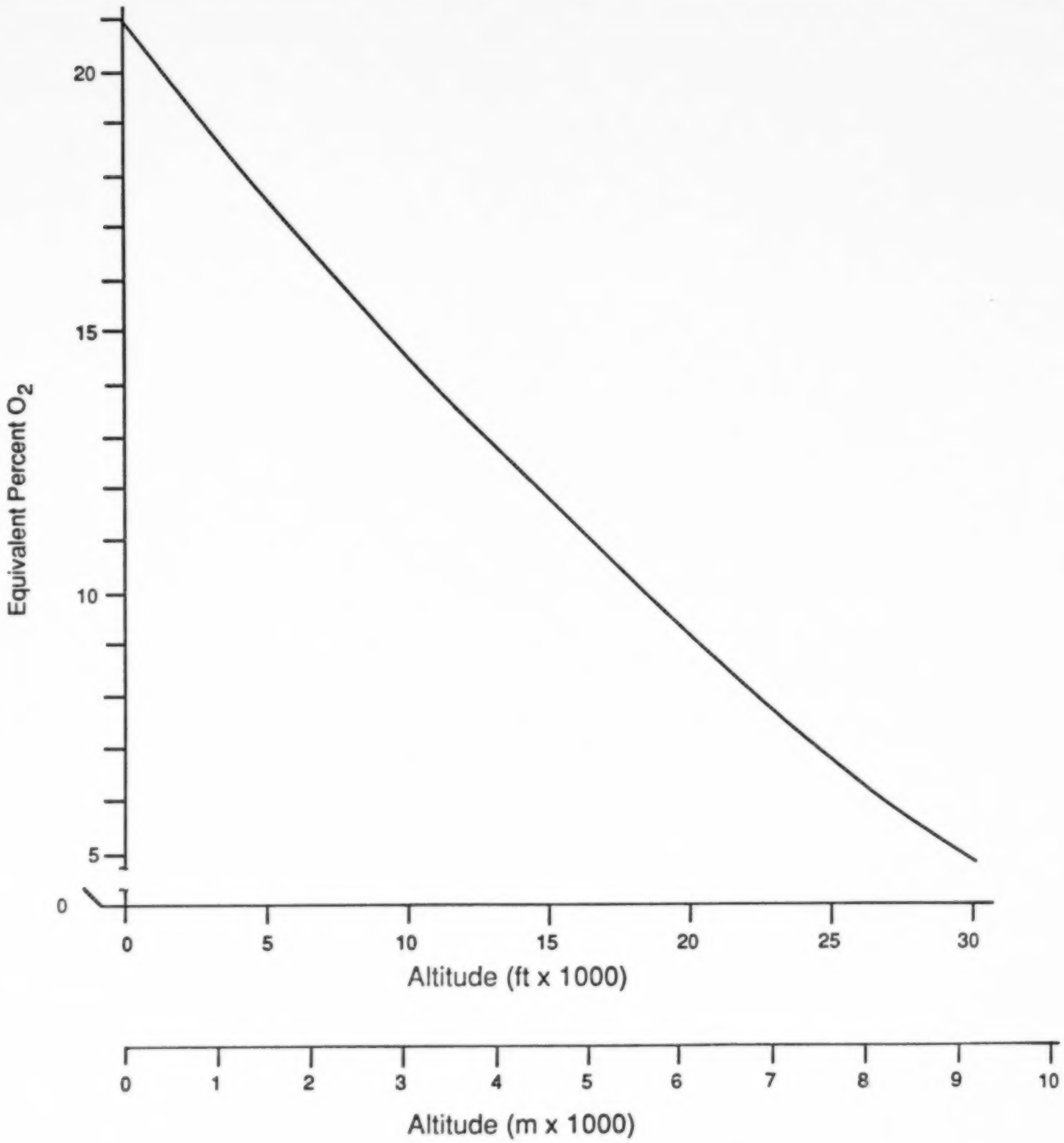

Figure 4. Nomograph for conversion of altitude to equivalent O_2 concentration in air.

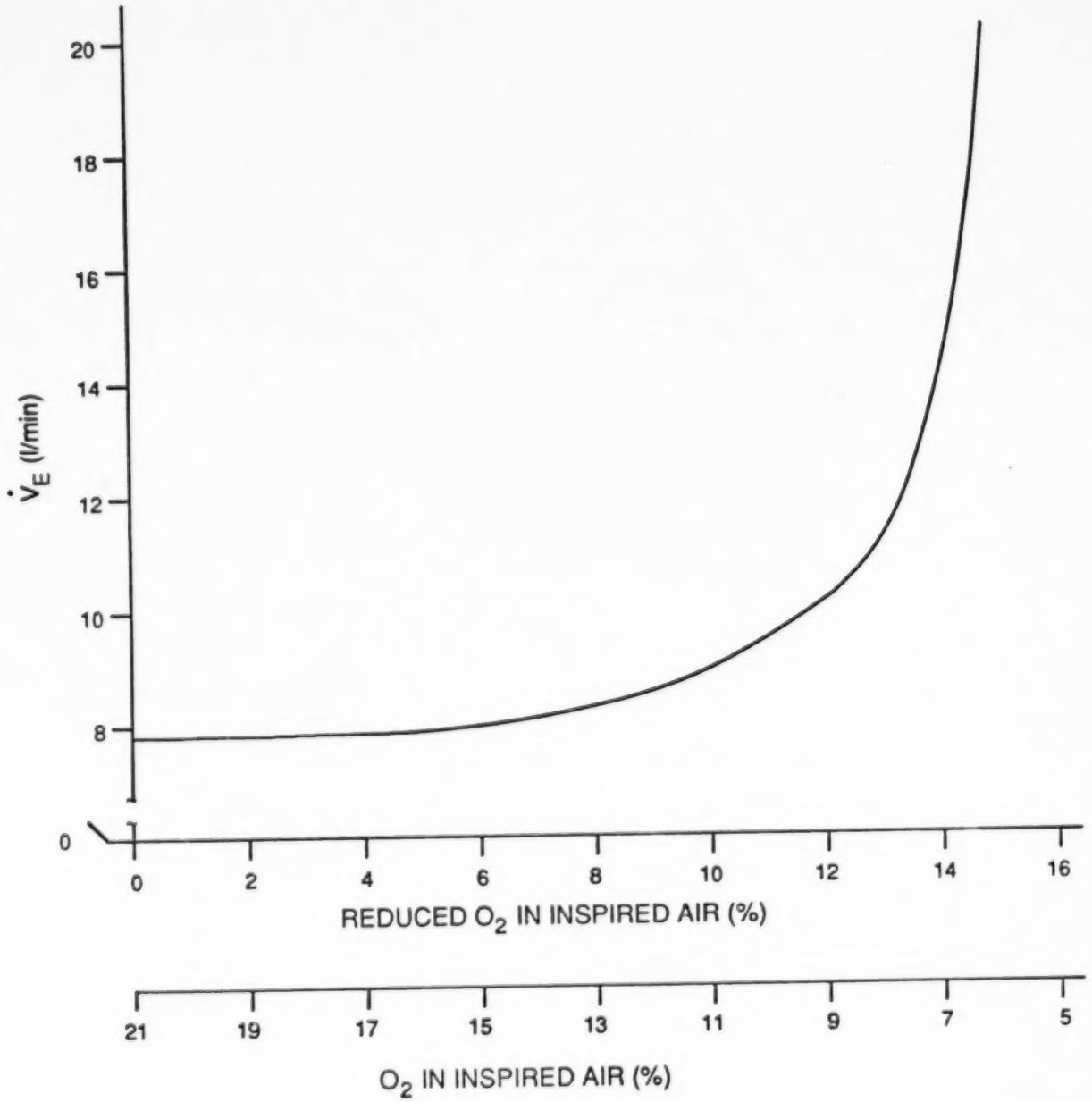

Figure 5. Effect of O_2 deficit on $\dot{V}_E$. Constructed from data published by Dripps and Comroe (1947).

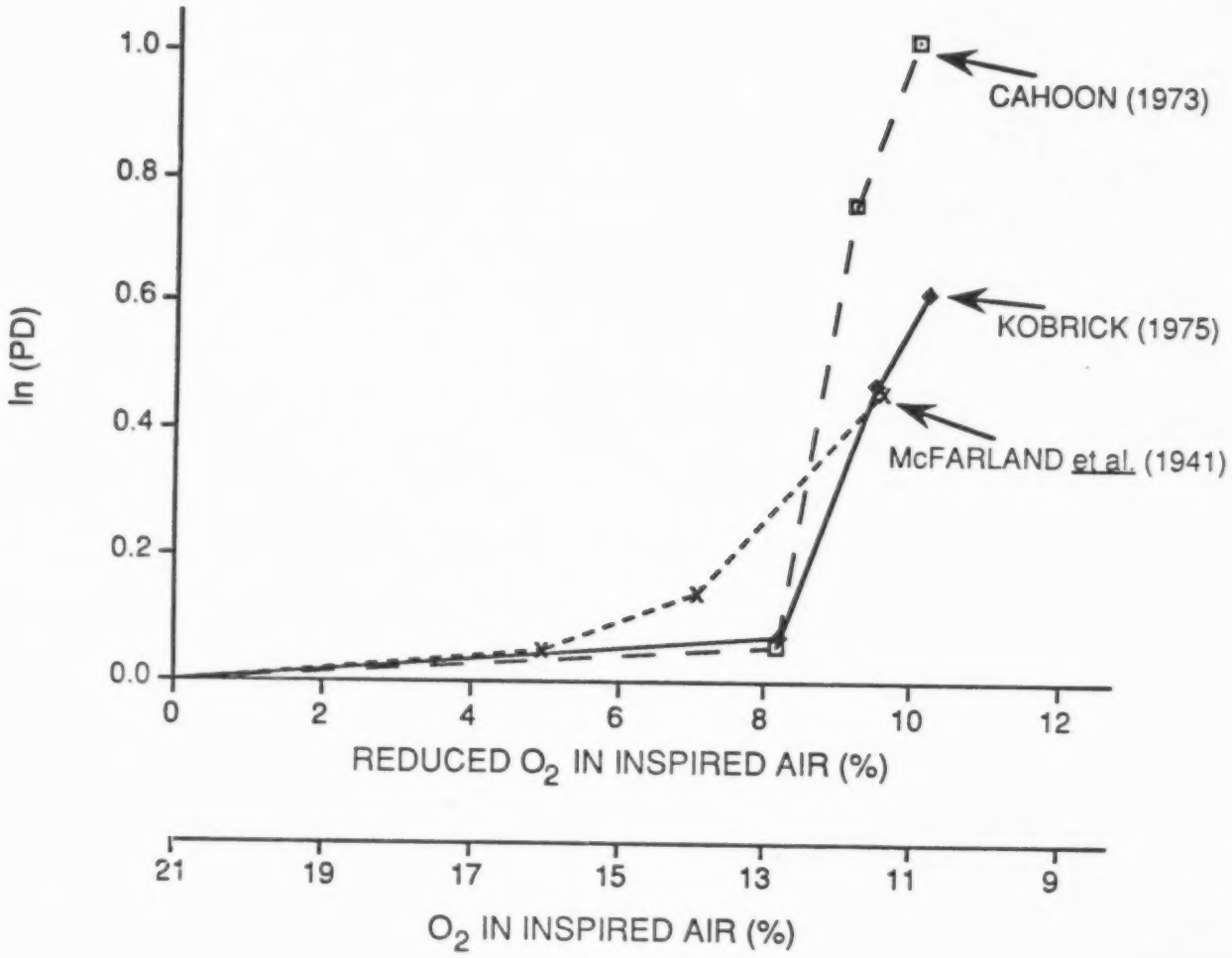

Figure 6. Effects of hypoxic hypoxia on various visual tests and vigilance. Data for McFarland et al. were obtained by averaging the last five values in their dark adaptation curves in their Figure 1. Data for Kobrick were read directly from his Figure 3 for the 12° stimuli reaction times. Data for Cahoon were read directly from his Figure 1. All data were converted to the same scale using procedures given in Benignus et al. (1988b).